Decl. 4/24/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
CHATFIELD
Serial No. 09/527,919
Filed: March 17, 2000
For: HEPATITIS B VIRUS POLYPEPTIDES

DECLARATION

The Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Mark Page, declare as follows:

1. I am currently Senior Director of Immunology of Apovia Inc, a company which is located in both San Diego, California and Munich, Germany. Before that, I was Head of Celltech Medeva's Vaccine Research Unit in London, England. A copy of my curriculum vitae is attached. The work described in the patent application was carried out in Celltech Medeva's Vaccine Research Unit.

2. I have been asked to comment on the argument made by the Examiner in the "Official Action" of 18 October 2001 that the invention claimed in the patent application was obvious over Mimms et al (European Patent Application EP-A- 389983), Khan et al (International Patent Application WO 94/03615) and Shi et al (Vaccine 1995, Vol. 13, pp. 933-937). I have read the patent application in question, the Official Action and the references cited by the Examiner.

3. The invention that is the subject of the application in question relates to fusion

polypeptides comprising tetanus toxin fragment C (or a fragment thereof) fused to pre-S sequence of hepatitis B virus. The idea is that the tetanus toxin fragment C acts as a "carrier" for the pre-S sequence and promotes the induction of an immune response against the pre-S sequence.

4. At the time the invention was made, a very large number of carriers proteins were known to scientists working in the field. For example, the following had been used a carriers: keyhole limpet hemocyanin (KLH), gelatin, albumin, ovalbumin, casein, bovine gammaglobulin (BGG), erythtrocytes, lipopolysaccharide (LPS), caroboxymethyl cellulose, poly-DL-lysine, mycobacterial heat shock proteins, micelles, liposomes, virosomes, immune stimulating complexes (ISCOMs), proteosomes, β-galactosidase, bacterial outer membrane and periplasmic proteins, hepatitis B core antigen, hepatitis B surface antigen, retroviral Gag proteins, phage coat proteins, retrotransposon Ty protein p1, the B subunit of heat labile toxin of *E.coli* and the B subunit of cholera toxin.

5. The number of antigenic sequences which could potentially be linked to each of these carriers was even greater than the number of potential carriers. The international patent application cited by the Examiner, WO 94/03615 of Khan et al, itself lists a very large number of antigenic sequences in the passage bridging pages 5 and 6. It lists antigenic sequences of HIV such as HIV-1 and HIV-2, e.g. the CD4 receptor binding site from HIV; hepatitis A virus; hepatitis B virus; human rhinovirus such as type 2 or type 14 rhinovirus; herpes simplex virus; poliovirus type 2 and 3; foot-and-mouth disease virus (FMDV); rabies virus; rotavirus; influenza virus; coxsackie virus; human papiloma virus (HPV); such as HPV type 16 and the E7 protein thereof and fragments of the E7 protein; simian immunodeficiency virus (SIV); *Bordetella pertussis* such as the P69 protein and filamentous heamagglutinnin (FHA); *Vibrio cholerae*; *Bacillus anthracis*; *E.coli* such as the B subunit of heat labile toxin (LTB), the K88 antigens and enterotoxigenic antigens; the cell surface antigen CD4; *Schistosoma manosi* such as p28 glutathione S-transferase antigens (p28 antigens); and flukes, mycloplasma, roundworms, tapeworms, *Chalmydia trachomatis*, and malaria parasites.

6. Thus, there were a vast number of combinations of carrier protein and antigenic sequence that could in theory have been put together by a scientist working in the field. I am not aware of any particular reason why a scientist would have chosen to put together fragment C and pre-S of hepatitis B out of all the other possible combinations that could potentially have been put togther. The references cited by the Examiner, EP-A-389983 of Mimms, WO 94/03615 of Khan et al and Shi et al, were not references which were high profile references in the field and I cannot see any particular reason why a scientist would have put the three of them together.

7. It was far from obvious that the combination of fragment C and pre-S sequence would induce a good antibody response against the pre-S sequence. The design of immunogens is an empirical art. It is difficult or impossible to predict in advance whether a particular polypeptide will induce a good immune response such as an antibody response. In order to find out whether a polypeptide will induce such a response, it is necessary to make the polypeptide and test it in animal models. It is generally not possible to predict in advance with any reasonable degree of certainty whether a given polypeptide will work or not.

8. The unpredictability of the art manifests itself in the Shi et al paper cited by the Examiner. Shi et al describes fusion of cholera toxin B subunit (CTB) to pre-S2 epitope. The fusion protein produced an extremely low antibody titre against the pre-S2 region. This is clear from, for example, Figure 7 on page 936 of Shi et al. The Figure shows that the peak antibody titre against CTB was about 5000, whereas the peak titre against pre-S2 was only about 140. A different scale had to be used for the anti-pre-S2 titre compared to that for the anti-CTB titre in order to present the anti-pre-S2 titre on the graph! The peak anti-pre-S2 titre was about 35 times less than the peak anti-CTB titre.

9. Thus, Shi et al suggested that the invention claimed in the patent application was <u>not</u> likely to be successful. The cholera toxin B subunit used as the carrier in Shi et al is similar to fragment C of tetanus toxin in that both are both are parts of bacterial toxins that are used as carriers because they are potent immunogens. The fact that cholera toxin B subunit did not work would have suggested that other bacterial toxins such as fragment C may not work.

10. The discussion section of Shi et al on pages 936-937 puts forward various possible reasons for the extremely low titre of pre-S2 antibody but does not reach any firm conclusions. It was apparently not clear to the authors of Shi et al why the titre was so low.

11. In contrast to Shi et al, the data in the patent application in question show that a good antibody response can be induced against pre-S by the fusion proteins that are the subject of the application. For example, the results presented in Figure 3B of the application show that, seven days after a booster dose, the fusion proteins induce a good antibody titre against a pre-S1 peptide. The titre is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2B). These results would not have been expected from a reading of Shi et al and the other references mentioned by the Examiner.

12. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of this Declaration, the patent application, or any patents issuing thereon.

Declared this 9th day of April 2002

Mark Page, PhD.

CURRICULUM VITAE

PERSONAL DETAILS

Name:	Mark Page
Date of birth:	4th November 1957
Nationality:	British
Marital status:	Married, 2 children

APPOINTMENTS

August 2001-date	Senior Director of Immunology, Apovia Inc., 11125 Flintkote Ave., San Diego, CA 92121 and Fraunhoferstr. 10, 82152 Martinsried, Munich, Germany
March 2001 – July 2001	Part-time consultancy work.
March 1997 – Feb. 2001	Head of Vaccine Research Unit, Celltech-Medeva, Dept. Biochemistry, Imperial College, Exhibition Road, London SW7 2AY
Dec. 1995 - March 1997	Senior Scientist, Vaccine Research Unit, Medeva, Dept. Biochemistry, Imperial College, Exhibition Road, London SW7 2AY
Sept. 1988 - Nov. 1995	Scientist, Division of Imunobiology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Hertfordshire.
Sept. 1985 - Aug. 1988	ARC Post Doctoral Research Fellow, Department of Anatomy, University College London, Gower Street, London.
Oct. 1983 - Sept. 1985	MRC Post Doctoral Research Fellow, Department of Anatomy, St. George's Hospital Medical School, Tooting, London.

ACADEMIC HISTORY

Sept. 1979 - Sept. 1983	Department of Zoology, University College, Swansea, Wales. Ph.D.: Immunology of Cyclostomes

Sept. 1976 - July 1979	University College, Swansea, Wales. Degree: B.Sc. (Hons) Zoology (Upper second)
1969 - 1976	Barton Peveril Grammar School, Eastleigh, Hants. A levels: Biology, Chemistry and Physics

MANAGERIAL / COMMUNICATION / ADMINISTRATION SKILLS

Management of and responsibility for all immunology projects at Apovia. Management of staff at Apovia's Munich operations. Responsibility for strategic operation of Apovia's product pipeline reporting to CEO.

Management of research laboratory (resources, budget (£850k pa), scientific activities) and direction of its activities (10 staff). Generation and selection of recombinant DNA vaccine candidates for phase I clinical trial evaluation. Antigen and epitope discovery using animal and in vitro human sample models.

Input and advise on company policy and strategic decisions for vaccine development through positions on management executive committee and project teams.

Interaction with external academic and industrial groups at senior level and strategic decision making on potential collaborations and licensing opportunities. Maintenance of collaborations with third parties through regular meetings to decide on direction and policy.

Presentation of Medeva development pipeline to analysts in London and New York.

Publication of results in scientific journals.

Filing of patents from research data. Interaction with patent attorneys.

Writing business plan for start up company (potential spin out from Celltech-Medeva). Liaising with Venture Capitalists to raise seed funding for start up.

LICENSING SKILLS

Provision of data reports generated from scientific analyses carried out by the Unit I manage and for inclusion in a license application for a new hepatitis B vaccine (Hepacare) that was subsequently approved by the EMEA (March 2000). Full review of the above license application before submission.

SCIENTIFIC SKILLS

Cell Biology:	Monoclonal antibody production, aseptic techniques, handling category II/III pathogens, virus cultures, virus neutralization assays, electron microscopy, cryostat sectioning, histology, histochemistry.
Biochemistry:	Protein purification and identification, electrophoresis, isoelectric focusing, chromatography including HPLC and FPLC, peptide synthesis.
Immunochemistry:	Immunofluorescence, RIPA, immunoblotting, ELISA, IRMA, RIA, immunohistochemistry, immunocytochemistry, antibody preparation and purification, antibody affinity chromatography.
Immunology:	T cell proliferation assay, cytotoxic T cell assay, antibody subclass determination.
Molecular Biology:	Gene cloning, PCR, RNA/DNA sequencing, recombinant DNA protein expression and purification.

REGULATORY AFFAIRS / QUALITY ASSURANCE EXPERIENCE

Consultant for both UK Medicines Control Agency and European Community National Agencies on licence applications for imunoglobulins and monoclonal antibodies when at NIBSC.

Responsibility for control of all UK licensed immunoglobulin products and issue of batch release certificates when at NIBSC.

Quality Co-ordinator, Study Director and Audit Officer responsibilities for implementing, operating and maintaining a Quality System at NIBSC in accordance with the NAMAS Accreditation Standard (BS7501; EN45001).

Certified Internal Quality Auditor for auditing to ISO 9000.

OTHER

Clean driving licence, computer literate (MicroSoft Office Suite, Outlook).

REFEREES

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PUBLICATIONS

1. Page, M. & Rowley, A.F. (1982). A morphological study of pharyngeal lymphoid accumulations in larval lampreys. Dev. Comp. Immunol. **Suppl. 2**, 35-40.
2. Page, M. & Rowley, A.F. (1983). A cytochemical, light and electron microscopical study of the leucocytes of the adult river lamprey, *Lampetra fluviatilis* (L. Gray). J. Fish Biol. **22**, 503-517.
3. Page, M. & Rowley, A.F. (1984). The reticulo-endothelial system of the adult river lamprey, *Lampetra fluviatilis* (L): the fate of intravascularly injected colloidal carbon. J. Fish Dis. **7**, 339-353.
4. Rowley, A.F. & Page, M. (1985). Ultrastructural, cytochemical and functional studies on the eosinophilic granulocytes of larval lampreys. Cell Tiss. Res. **240**, 705-709.
5. Rowley, A.F. & Page, M. (1985). Lamprey melano-macrophages: structure and function. *In*: Fish Immunology (eds. M.J. Manning & M.F. Tatner), pp.273-284. London: Academic Press.
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9. Page, M. & Ashhurst, D.E. (1987). The effects of mechanical stability on the macromolecules of the connective tissue matrices produced during fracture healing. II. The glycosaminoglycans. Histochem. J. **19**, 39-61.
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52. Page, M. & Robin Thorpe. 1998. IgG purification. In: Methods in Molecular Biology : Immunochemical protocols. Ed. Pound, J.D., Humana Press. Totowa, New Jersey, pp. 113-119.
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55. Page, M., Jones, C.C. & Bailey C. (in press). Review: A novel recombinant triple antigen hepatitis B vaccine (Hepacare). Intervirology
56. Jung, M.-C.,Gruner, N., Zachoval, W.,Schraut, W., Gerlach, T., Diepolder, H., Schirren, A., Page, M., Bailey, J., Birtles, E., Whitehead, E., Trojan, J., Zeuzem, S. & Pape, G.R. (submitted). Therapeutic vaccination in chronic hepatitis B: qualitative and quantitative analysis of the hepatitis B virus specific response. J. Clin. Invest.

PATENTS

1. Designing immunogens. UK patent application 0007789. (1PCT/GB00/03857).
2. Modification of hepatitis B core antigen. UK patent application 0015308.0
3. A major histocompatibility complex antigen for use as a vaccine against an immunodeficiency virus - W09401130.